REMARKS

Claims 1-13 and 15-31 are pending in this application. Claims 1-12 and 24-28 are withdrawn from consideration. Claims 13 and 15-19 have been amended herein. Claim 14 has been cancelled and claims 29-31 are newly added.

Objections to the claims

Claim 19 has been objected to for the recitation of parentheses in the final line. Recitation of "(ATP-binding cassette A1)" has been deleted from claim 19. Withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C. §112, 1st paragraph (enablement)

The Examiner rejects claims 13 and 19-23 under 35 U.S.C. §112, 1st paragraph for lack of enablement with on the assertions that,

a) the specification is only enabled for testing for liver damage and oxidative stress associated with paraoxonase activity, as disorders which detrimentally affect the protective effect of HDL; and

b) the specification is not enabled for protection from the risk of cardiovascular disease because "protect" would be interpreted as 100% prevention.

Claim 13 has been amended to incorporate the subject matter of claim 14, which was not rejected. As such, the point raised by the Examiner regarding the disorder in question has been addressed. However, in point a), above, the Examiner also asserts that the specification is only enabled for liver damage and oxidative stress associated with paraoxonase activity. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Paraoxonase activity is only one form of expressed oxidative stress. The present invention is directed to liver damage and oxidative stress, in general, not exclusively associated with paraoxonase activity. Reduced paraoxonase activity is a consequence of liver damage. As such, assessments of paraoxonase activity, expression thereof and mutations thereof can be used to assess liver damage. In addition, oxidative stress causes oxidative damage in the liver and is, thus, one source of liver damage (eg. Parola M. et al. "4-hydroxy 2,3-alkenals as molecular mediators of oxidative stress in the pathogenesis of liver fibrosis" Int. J. Mol. Med. (1999) 4(4):425-432). In addition, a deterioration of antioxidative defenses causes a predisposition to oxidative damage in the liver. (e.g. Sokol et al. "Antioxidative defenses in metal-induced liver damage" Semin. Liver Dis. (1996) 16(1):39-46; Comporti et al. "Glutathione depletion: its effects on other antioxidant systems and hepatocellular damage." Xenobiotica

(1991) 21(8):1067-1076).

It was well-known in the art at the time of the present invention that the paraoxonase enzyme is but one example of antioxidative defense systems in the liver. It was further well-known in the art at the time of the invention how to assess liver damage. For example, the general textbook of clinical chemistry, Fundamentals of Clinical Chemistry, ed. N.W. Tietz, W.B. Saunders Co. (publ.), Philadelphia, PA (1976), states that gamma-glutamyltransferase may be used as a test of liver function and liver damage. Similarly, Pratt et al. "Evaluation of abnormal liver-enzyme results in asymptomatic patients." N. Engl. J. Med. (2000) 342(17):166-71, teach that alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyltransferase may all be used as screens for liver damage. In addition, oxidative stress measurements have been used widely in assessing liver damage. As such, the invention is fully enabled as claimed for assessing liver damage and oxidative stress.

As noted above, in point b), the Examiner further rejects claim 13 with the assertion the specification is not enabled for protection from the risk of cardiovascular disease because "protect" would be interpreted as 100% prevention. Claim 13 has been amended to more clearly recite, "Method of treatment of an

individual to reduce the risk of cardiovascular disease..." As such, the invention does not require that the method necessarily results in 100% prevention.

The claimed invention is thusly fully enabled and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, 1st paragraph (written description)

On pages 6 and 7 of the Office Action, the Examiner rejects claims 13, 14 and 16 under 35 U.S.C. §112, 1st paragraph, for lack of written description. More specifically, the Examiner asserts that the specification fails to provide adequate written description for the genotype mutations or polymorphisms that will influence the serum or plasma γ-glutamyltransferase activity or concentration, or mutations in the phase I and II enzymes.

Applicants believe that this rejection is misplaced and inappropriate to the present invention. 35 U.S.C.§112, 1st paragraph requires that,

> The specification shall contain a written description **of the invention...** (emphasis added)

Mutations and polymorphisms per se are not part of Applicants' invention and Applicants are not claiming the mutations and polymorphisms. The present invention is drawn instead to a method

which may, as one approach, use genotyping for mutations. As such, the claimed invention is adequately described.

The fact that mutations and polymorphisms per se are not part of the present invention is supported by the fact that many such mutations and polymorphisms are known in the art and therefore would not need to be described in the specification. For example, information regarding mutations of genes encoding γ-glutamyltransferase was readily available through OMIM (http://www.ncbi.nlm.nih.gov//Omim/searchomim.html; entries *231950 and *137181), as well as other databanks at the time of the invention. Mutations of the phase I (CYP450) and phase II enzymes were also know at the time of the invention (see for example, OMIM entry 108330). Withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C. §112, 2nd paragraph

Claims 13-23 have been rejected under 35 U.S.C. §112, 2nd paragraph as being unclear. More specifically, the claims have been rejected for the reasons detailed on pages 7-9 of the Office Action. Claims 13, 16 and 19 have been amended to address these issues. As such, withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. §102 for lack of novelty

Claims 13-14 and 19-21 have been rejected under 35 U.S.C. §102(b) for lacking novelty over "Facts (Drug Facts and Comparison)" pages 1082-1092 and 1100. The Examiner relies on the "Facts" as teaching certain drugs, (gemfibrozil and pravastin) are useful for reducing the risk of coronary heart disease, but should not be given to patients with liver damage. The Examiner asserts that based on the indicated contraindications with gemfibrozil and pravastin, doctors would necessarily test for liver damage prior to administering these drugs to heart patients. The Examiner asserts, that doctors would therefore be inherently practicing the present invention. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The invention as most broadly encompassed by claim 13 is drawn to a method of treatment of an individual to reduce the risk of cardiovascular disease, by testing the individual for a disorder which reduces the protective effect of HDL compared to the level of the protective effect of HDL in the absence of the disorder, identifying and selecting the patient population that is free of the disorder, and treating the selected patient population to increase the HDL or HDL cholesterol level, wherein said disorder is liver damage or oxidative stress.

The Examiner relies on the disclosure in "Facts (Drug Facts and Comparison)" as inherently anticipating the present invention. However, "Facts (Drug Facts and Comparison)" regards liver dysfunction as a contraindication, whereas the present invention is directed to liver damage as a disorder, per se. The disclosure in "Facts (Drug Facts and Comparison)" pertains to clear and severe liver dysfunction, whereas the "liver damage" in the present invention refers to even a small increase in liver enzymes.

"Facts (Drug Facts and Comparison)" teaches that patients with hepatic or severe renal dysfunction should not take gemfibrozil, i.e hepatic dysfunction is a contraindication for gemfibrozil. However, hepatic dysfunction is not the same as "liver damage." "Hepatic dysfunction" refers to advanced states of liver damage, such as liver cirrhosis (e.g. biliary cirrhosis). The present invention, on the other hand, demonstrates that drugs such as gemfibrozil loose their benefit with mild liver damage, even with just liver activation, where is there is no hepatic dysfunction.

The cut-off of γ-glutamyltransferase in the experimental section, which was used as a measure of liver function, was as low as 60 U/L. 60 U/L is the upper normal limit, whereas hepatic dysfunction is typically defined as three-times the upper normal limit.

"Facts (Drug Facts and Comparison)" also teaches that a contraindication to HMG-CoA reductase inhibitors is "active liver disease or unexplained persistent elevated liver function test." As with liver dysfunction, these states go far beyond the liver damage of the invention. In addition, the present invention is not concerned with contraindications associated with lipid drugs, but rather the use of an assessment of liver function, liver activation, liver damage or the disposition of liver damage as a method of selecting a proper lipid drug.

The present invention is not concerned with contraindications associated with drugs. One skilled in the art would readily know not to give a drug to a patient where there is a contraindication. Thus, one skilled in the art would know not to administer contraindicated drugs to patients having liver dysfunction, such as cirrhosis. However, there is no contraindication to giving lipid drugs to patients who do not have liver dysfunction. Thus, one skilled in the art, prior to the present invention, would conclude that unless a patient had liver dysfunction, lipid drugs are suitable a treatment to elevate HDL in a patient. However, the present inventors have determined the even with mild liver damage, far below that of liver dysfunction and associated with just a small to moderate elevation in liver enzymes, HDL elevating drugs may loose their beneficial effects. There is no disclosure or

suggestion of this property in "Facts (Drug Facts and Comparison)". Nor is there any suggestion or disclosure of the screening method of the present invention in "Facts (Drug Facts and Comparison)", which is only concerned with liver dysfunction. As such, the method of the present invention is distinguished from "Facts (Drug Facts and Comparison)" and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103 for obviousness

Claims 13-15, 17-19 and 22-23 have been rejected under 35 U.S.C. §103 as being obvious over Lyons et al. and the Merck Manual combined with Boden, Navab et al., Traub and "applicant's admission", i.e. the disclosure in the specification.

Lyons et al. and the Merck Manual are relied on for teaching ways to increase the HDL levels. The references fail to teach the exclusion of patients having disorders affecting HDL protective activity.

Boden is asserted to teach the connection between increased HDL with reduced risk of heart disease. Navab et al. is asserted to teach that HDL activity is dependent on paraoxonase and PAF acetylhydrolase. Navab et al. is also asserted to teach that with certain conditions the paraoxonase and PAF acetylhydrolase levels decrease but the HDL level remains the same. Traub is relied on

for teaching the use of GGT levels as an indication of liver disease.

Finally, the Examiner relies on the disclosure in the specification, citing to Perova et al., for teaching that with high alcohol drinkers, high levels of HDL do not result in reduced risk of coronary heart disease.

The Examiner asserts that based on the combined teachings of the references, it would be obvious to a) generally increase the HLD levels to reduce the risk of heart disease and to also b) exclude patients with liver disease from such treatments because it was known that increasing HDL would not be an effective means of in patients with liver damage.

Applicants traverse this rejection and withdrawal thereof is respectfully requested. The present invention is not *prima facie* obvious over the cited references because the invention is not achieved or suggested by the combined teachings of the references.

Lyons et al. teaches that colestipol can enhance the HDL level, but does not teach any relationship with liver function or oxidative stress. The Merck Manual teaches that exercise can increase the HDL level, but also does not teach any relationship with liver function or oxidative stress. Similarly, Boden teaches that HDL is a risk factor for coronary heart disease, but does not teach any relationship with liver function or oxidative stress.

Navab teaches that the antioxidative effect of HDL is dependent on paraoxanase and PAF-a. Navab teaches an antioxidative effect of HDL, but not of protective effects of HDL against coronary heart disease. Traub simply discloses γ-glutamyltransferase as a test of liver function.

Finally, the Examiner relies on Perova et al. for achieving a suggestion of the invention. However, Perova et al. fails to suggest the present invention when combined with the other references. In Perova et al. (a copy of which is attached hereto), alcohol intake was one of many variables evaluated in the studies of the reference. Perova et al. concluded that in the Russian population, there is a lack of protective effects of HDL. There is; however, no teaching in the reference that the lack of protective effects of HDL was attributable to liver damage or liver function. The connection between the lack of protective effects of HDL discussed in the authors of Perova et al. and liver damage or liver function, was a hypothesis of the present inventors. As noted by the Federal Circuit:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would

> have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. In re Vaeck 20 USPQ2d 1438 (Fed. Cir. 1991).

The Court of Customs & Patent similarly instructed regarding Applicants' disclosure that in determining obviousness it is not permissible to include "knowledge gleaned only from applicant's disclosure", In re McLaughlin 170 USPQ 209 (Ct. Cust. & Pat. App. 1971). Any disclosure in the present specification regarding a connection between the lack of protective effects of HDL and liver damage or liver function is knowledge of the present inventors and thus, cannot be used determining the obviousness of the invention.

Thus, the conclusion reached by the Examiner on page 12 of the Office Action regarding the obviousness of the invention and motivation of one skilled in the art is incorrect. Assuming *arguendo* that one skilled in the art had the motivation to put the teachings of the references together, the conclusion reached would likely be the opposite of the invention.

The present inventors have shown that patients having liver disease do not benefit from treatments that increase HDL and thus the HDL protective effect. The present inventors have shown, for the first time, that lipid drugs loose their efficacy if there is liver damage. However, based on the teachings of the references,

one skilled in the art would more likely conclude that elevation of HDL would be more beneficial in those patients having low HDL compared to those already having high HDL. Indeed, the conclusion reached by the Examiner in the final paragraph of page 12, spanning page 13 is incorrect. The Examiner states, "One of ordinary skill in the art would have been motivated to employ colestipol in patients who is having alcoholic liver disease...." Thus, even the Examiner has reached the conclusion that is contrary to the invention. The Examiner states that it is obvious to treat a patient having alcoholic liver disease with a lipid drug. However, the present inventors have shown the exact opposite effect, i.e. that patients with liver damage do not benefit from lipid drugs. One skilled in the art would not have been able to conclude this unexpected finding of the inventors before the present invention, since prior to the invention the inverse relationship between the elevation of HDL in preventing coronary heart and liver damage was not known. As such, the invention is in no way suggested by or obvious over the references and withdrawal of the rejection is respectfully requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $55.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment(s): Perova et al., Ann. Epidemiol. (1995) 179-185
(with Information Disclosure Statement)

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